REMARKS

Rejection of Claims 66-82 under 35 U.S.C. § 102(e) as being anticipated by *Ebner, et al.*, U.S. 2003/0092133.

Claim 66-82 remain rejected under 35 U.S.C. § 102(e) as being anticipated by *Ebner et al.*, U.S. 2003/0092133 ("*Ebner et al.*"). The rejection has been made final.

In the last Office Action, dated April 6, 2005, the Examiner maintained the prior art rejection imposed in the prior Office Action dated June 21, 2004. The Examiner suggests that the *Ebner et al.* published patent application is entitled to a prior art date of September 10, 1998 based on its claim under 35 U.S.C. §119(e) to provisional application 60/099,805 ("'805 provisional"). The Examiner observes that the filing date of the '805 provisional predates the effective filing date determined to exist by the Examiner for the instant application, which appears to be based on the Examiner's conclusion that SEQ ID NO:3 and 4 were included in the provisional application 60/113,621 filed on December 23, 1998, but not in provisional applications filed prior to this date. The Examiner notes that the declaration filed on December 21, 2004 under 37 C.F.R. 1.131 is ineffective to overcome the Ebner reference because it is a U.S. patent application that claims the rejected invention.

Throughout prosecution of the present application, the Examiner has maintained that *Ebner et al.* (both the currently pending '133 publication and the abandoned divisional US 2003/0003545) disclose a polypeptide of IL-21, which has the amino acid sequence of SEQ ID NO:29, and is 100% identical to SEQ ID NO:3 of the present invention. The Examiner has also asserted that Ebner teaches a pharmaceutical composition comprising the polypeptide and a kit comprising the composition. The Examiner has taken the position that functional limitation recited in the presently rejected claims, of inducing the production of TNF-a in THP-1 cells and for treatment of a degenerative cartilaginous disorder are either an inherent property of the same composition, or an intended use of the claimed composition, and do not alter the nature of the composition. The Examiner also notes that the informational content of the printed matter is given no weight and does not render the article patentable distinct from the teachings of Ebner. Furthermore, the Examiner asserts that Ebner teaches a fusion protein comprising said

polypeptide fused to antibody domains such as an antibody Fc region. See February 24, 2003 Office Action, page 3 (Paper no. 16).

The Examiner's position appears to be that by merely disclosing a nucleotide sequence, without disclosing any information regarding any biological role, function, or activity of either the nucleotide sequence or the polypeptide encoded thereby, the *Ebner et al.* disclosure fulfills the requirements for anticipation of the present claims under 35 U.S.C. § 102(e). Applicant traverses this conclusion of law. In particular, as set forth in previous responses, Applicant maintains that in order to be given effect under § 102(e), the claims of the reference patent or published patent application must be supported in the manner required by 35 U.S.C. § 112 in the priority application whose date is relied upon to establish the prior art status of the patent. *See In re Wertheim*, 646 F.2d 527, 209 USPQ 554 (CCPA 1981); and MPEP 2136.03, sub-heading IV. If the priority application fails to support the claims at issue (i.e., being rejected) in the manner required by § 112, the reference is not entitled to have prior art under § 102(e) as of the filing date of that priority application. In the present case, the provisional application to which *Ebner et al.* claim the benefit does not provide a specific, substantial and credible utility for the claimed subject matter. As a consequence, the *Ebner et al.* provisional does not satisfy the "how to use" prong of the § 112 requirements and is not entitled to the filing date of the provisional application. Thus, *Ebner et al.* is not prior art under § 102(e). Further elaboration is provided below.

Applicant's observations on the scientific credibility and content of the *Ebner et al.* disclosure.

Applicant observes the following deficiencies of the *Ebner et al.* disclosure, which are numerous and include the following:

- The homology analysis set forth in the *Ebner et al.* disclosure is essentially meaningless to a person of skill in the art. *Ebner et al.* note that using BLAST and Megalign analysis, the amino acid sequences identified in their disclosure were each found to be "highly homologous" to several members of the Interleukin family. Particularly, the disclosure notes that SEQ ID NO:2, SEQ ID NO:4, and SEQ ID

NO:29 as disclosed in the '805 provisional application contain at least four domains homologous to the translational products of the human mRNA for Interleukin (IL)-20, IL-17, the murine mRNA for IL-17 (mIL-17), and the human viral mRNA for IL-17 (vIL-17). The disclosure also notes that the full length sequence (SEQ ID NO:29) of the identified IL-21 molecule shares a "high degree" of amino acid sequence identity with IL-20, IL-17, mIL-17, and vIL-17 in three conserved domains. From this, *Ebner et al.* conclude that "[b]ecause each of these IL-17 and IL-17- like molecules is thought to be important immunoregulatory molecules, the homology between these IL-17 and IL-17-like molecules and IL-21 and IL-22 suggest that IL-21 and IL-22 may also be important immunoregulatory molecules." (See '805 provisional, pages 10-11). While *Ebner et al.* provides an amino acid sequence comparison of the IL-21 protein with the known sequences of IL-17 and related molecules (See '805 provisional, Figures 3A and 3B), the reference does not state the percent identity that is shared.

Ebner et al. present a highly questionable homology analysis – both with respect to the degree and nature of the homology to IL-17. Applicant's own analysis reveals that the polypeptide resulting from the identified nucleotide sequence shares only a 26-28% amino acid identity with IL-17. (See page 48 and Figure 7A of the present application). *Ebner et al.* acknowledge that IL-17 exhibits pleiotropic biological activities on various cell types, including its role in stimulating the expression of other cytokines such as IL-6, IL-8, G-CSF, Prostaglandin E (PGE_2), and Intercellular Adhesion Molecule (ICAM)-1. (See '805 provisional, page 2). However, there is nothing in *Ebner et al.* to indicate that the biological activities of IL-17 will be shared by the claimed polypeptide, especially when considering the low degree of amino acid sequence identity shared between the molecules. Thus, the observed degree of sequence homology to IL-17 and related molecules conveys no meaningful information concerning the biological role, function or activity of the claimed polynucleotide and polypeptide sequences.

- *Ebner et al.* fail to disclose any specific and substantial utility for the polynucleotide or polypeptide corresponding to their identified sequences. The uses that *Ebner et al.* disclose for the polynucleotide and polypeptide corresponding to IL-21 are merely generic uses for *all* polynucleotides and polypeptides. For instance, the disclosure states that the polynucleotides in question can be used for chromosome mapping, to control gene expression through triple helix formation or antisense DNA or RNA, for DNA-based identification techniques, and "at the very least" as molecule weight markers, as diagnostic probes, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response (see '805 provisional, pages 48-52). These applications and techniques, however, are not specific for the polynucleotides disclosed by *Ebner et al.* Indeed, the same uses can be stated for *any* polynucleotide sequence. Similarly, *Ebner et al*'s disclosed uses for the polypeptides – such as to assay protein levels, to treat some unknown disease to replace absent or decreased levels of the polypeptide, as molecular weight markets, or to raise antibodies to the polypeptide – are generally applicable to *any* polypeptide molecule (see '805 provisional, pages 52-54).

- The biological activities and disease states that *Ebner et al.* identifies with the claimed polynucleotides and polypeptides are merely speculative and nonspecific. Among the supposed "biological activities" of IL-21, *Ebner et al.* disclose that the protein "modulates" IL-6 secretion from NIH-3T3 cells. The reference, however, makes no indication about whether IL-6 amounts increase or decrease – or remain unchanged – as a result. Instead, the disclosure merely proposes the use of a known assay to determine the level of IL-21-mediated IL-6 secretion. A similar assay is referenced to determine whether IL-21 modulates lymphocyte proliferation without any indication as to the actual effect of these proteins. (See '805 provisional, pages 54-55). The same holds true for the other activities disclosed by *Ebner et al.*, including the immune activity, chemotaxic activity, and binding activity, that may (or may not) be associated with the protein. (See, e.g., '805 provisional, pages 56-58 and 61-63). These disclosures of biological activity are merely speculative, unsupported

by biological data, and scientifically meaningless to one of skill in the art. Applicant notes in this regard that the various assays that *Ebner et al.* propose in their Examples are completely prophetic and contain no actual biological data relating to the IL-21 protein (See '805 provisional, Examples 13-20). To the extent that *Ebner et al.* provide any tissue distribution data through Northern blot analysis, it shows that the Il-21 protein is expressed in variety of tissues (i.e., thymus, adrenal cortex, spleen pancreas, lymph node, PBL, fetal liver, adrenal medulla, thyroid, small intestine, stomach, and heart) with no known correlation to particular disease states (See '805 provisional, page 66). This disclosure does not suggest or teach that the IL-21 protein can be used in any useful manner for diagnosis or treatment.

- *Ebner et al.* merely speculate that IL-21 can be used in the treatment of a long and varied list of conditions from inflammation to cancer to AIDS. No support is provided in *Ebner et al.* for the suggestion that the IL-21 polypeptide or antibodies to them can be used in the variety (dozens) of therapeutic applications recited (*See, e.g.*, '805 provisional, pages 56-60). Indeed, *Ebner et al.* appear to have based this prediction on information known about *other* interleukin family members, *not* the particular IL-21 polypeptide. If anything, the recitation of such a laundry list of varied and biologically diverse conditions suggest that *Ebner et al.* in fact had no idea of what IL-21 could actually be used for.

Thus, while *Ebner et al.* discloses certain sequence structure information for the IL-21 molecule, it utterly fails to disclose any information that would credibly describe any biological role, function or activity of these polypeptides. Instead, the disclosure speculates as to possible functions or activities that they might possess, but in a way that is so generalized and abstract as to be meaningless to a person of ordinary skill in the art. Indeed, there is no data provided in the *Ebner et al.* disclosure that can reasonably establish *any* biological function or activity of the putative cytokine, much less information that could establish a specific role of the nucleic acid, polypeptide, or its antibodies. Such a disclosure, which provides no experimental data establishing a biological role for the polynucleotide and polypeptide, is *scientifically* meaningless

to a person of skill of the art. For the reasons stated below, it should therefore not qualify as prior art.

***Ebner et al.* is legally insufficient to anticipate the presented claims**

Applicant maintains that the scientifically deficient disclosure of *Ebner et al.* renders it legally insufficient to anticipate the rejected claims. In particular, the *Ebner et al* disclosure does not provide an accurate or unequivocal characterization of any biological function, activity or role of the claimed nucleic acid molecule. Instead, it merely discloses a polynucleotide sequence and speculates as to its biological function, role and activities.

Applicant submits that the proper legal standard for measuring the sufficiency of a U.S. patent for anticipation under 35 U.S.C. § 102(e) is that articulated by the Court of Customs and Patent Appeals in *In re Wertheim and Mishkin*, 209 USPQ 554 (CCPA 1981); namely, that a U.S. patent (in this case, patent publication) can anticipate under 35 U.S.C. § 102(e) as of a particular date only to the extent that there is a sufficient disclosure under 35 U.S.C. § 112, first paragraph, for the subject matter at issue (i.e., the subject matter of the claims being rejected as anticipated under §102(e) by the patent).

In *Wertheim*, the court addressed the specific question of the effective date – for prior art purposes – of a patent under 35 U.S.C. §§102(e) where the patent claimed the benefit of an earlier application under 35 U.S.C. §120. The court found that the §102(e) effective date of the patent was limited to that subject matter in the patent that could satisfy the requirements of 35 U.S.C. § 112, first paragraph, relative to the claims being rejected. Thus, the court recognized that a patent should be entitled to a prior art effect under § 102(e) *only as to subject matter that was disclosed in a manner that would be sufficient under § 112, first paragraph. Wertheim* states at 539 that "... the application, the filing date of which is needed to make a rejection, must disclose, pursuant to §§120/112, the invention claimed in the reference patent." If the priority application fails to provide a sufficient disclosure, it may not serve as the basis for establishing a prior art effective date under § 102(e) for the patent or published application.

For the numerous reasons set forth above, the *Ebner et al.* patent does not provide an adequate disclosure under §112, first paragraph of the subject matter of the presently rejected claims. Therefore, *Ebner et al.* is not prior art under § 102(e) and the instant rejection should be withdrawn.

It is also well established that enablement requirement of § 112 incorporates the utility requirement of § 101. *See In re Ziegler*, 992 F.2d 1197, 1200-01 (Fed. Cir. 1993); MPEP § 2107.01. Therefore, if a reference provides no specific, substantial and credible utility for the claimed subject matter, it fails to satisfy the requirements of § 112 and cannot properly be considered as prior art under § 102(e). In this case, application of the PTO's own utility guidelines clearly shows that *Ebner et al.* cannot support the present claims because it is incapable of establishing a specific, substantial and credible utility for the presently claimed subject matter. While there is no *per se* rule regarding homology-based assertions of utility, the Guidelines direct Examiners to take into account both the nature and the degree of homology recited in the application. Applicant notes the very low degree of homology (no more than about 28%) between the claimed polypeptide, and IL-17 and related cytokines. Even the minimal amount of homology that is provided is simply the result of data mining and cannot be used to confirm whether the proteins share any biological activities. No actual comparison of the structure or biological activities of the proteins is provided. *Ebner et al.* thus cannot rely on its insufficient (both in terms of the degree and nature) homology analysis, particularly in the absence of experimental data characterizing the polypeptide at issue to confirm its predictions, in order to establish a specific, substantial and credible utility for a putative nucleic acid molecule which encodes said polypeptide.

Additionally for the reasons noted, the asserted uses, biological activities, and therapeutic applications disclosed by *Ebner et al.* are insufficient under § 101 because they qualify as neither "specific" nor "substantial" utility under Federal Circuit precedent. This principle was most recently reaffirmed in *In re Fisher*, No. 04-1465 (Fed. Cir. 2005), where the Federal Circuit held that claims to nucleic acid sequences for which the corresponding biological function is unknown fail to satisfy the utility requirements. The only known uses disclosed by *Ebner et al.* are nonspecific ones such as "gene probe" and "chromosome marker," which the court

specifically found insufficient to qualify as utility in *Fisher*. As noted by the court, these represent "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *Fisher*, *13-14 (citing *Brenner v. Manson*, 383 U.S. 519, 535 (1966). Furthermore, the biological activities and disease states that *Ebner et al.* associate with the claimed polypeptides and polynucleotides are merely speculative and cannot establish utility. *Ebner et al.* does not definitively associate any particular activity to the polypeptide or polynucleotide sequences that are disclosed and certainly provides no *in vitro* or *in vivo* data to support its speculated utility.

The insufficient disclosure in *Ebner et al.* (i.e., the disclosure does not set forth a specific, substantial and credible utility for the nucleotide sequence and associated polypeptide), makes it impossible for the reference to satisfy the "how to use" prong of § 112 for the presently claimed subject matter. As a matter of law, then, because *Ebner et al.* fails to satisfy the requirements of § 101, it fails to provide an enabling disclosure under § 112 and cannot anticipate the rejected claims under § 102(e).

Additional Comments

For the reasons provided above, the present claims are believed to be in condition for allowance. If the Examiner believes any issues require further consideration, she is invited to contact the undersigned.

Respectfully submitted,
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